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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,443	COURTY ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *4-7,11-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8-10, 15-16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

1. Claims 1-19 are pending.

2. Applicant's election of Group 1 (claims 1-3, 8-10, 15-16 and 19) in the reply filed on October 17, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 4-7, 11-14, 17 and 18 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3, 8-10, 15-16 and 19, drawn to a peptide comprising the sequence of amino acid selected from the sequence 13-39 of the HARP factor or the sequence 65-97 of the HARP factor, a pharmaceutical composition comprising said peptide and one or more pharmaceutically acceptable excipient, a method for preparing a medicament comprising adding said peptide to a pharmaceutically acceptable vehicle, are being acted upon in this Office Action.

5. Claim 10 is objected to because "et" should have been "and".

6. Claim 15 is objected to because "angiogenesis ," should have been "angiogenesis,".

7. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

8. The disclosure is objected to because of the following informalities: (1) the specification is missing all the section heading, see guideline above and (2) the typographical errors such as "f actors" at page 3, line 30, "wit h" at page 4 line 15, "a nd" at page 4, line 18, "rhe umatoid" at page 16, line 14 and "posology" at page 18, line 30 need to be corrected.

9. The disclosure is further objected to under 37 CFR 1.821 through 1.825 for failure to supply a sequence identifier to all disclosed sequences. In particular, the sequence SDCGEWQWSVCVPTSGDCGLGTREGTR (SEQ ID NO: 2) at page 6 is consistent with the sequence SDCGEWQWSVCVPTSGDCGLGTREGTRT (SEQ ID NO: 2) in paper copy and computer readable copy of the sequence listing. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must provide a substitute computer readable form (CFR) copy of the sequence listing, a substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same, and where applicable, include no new matter, as required by 37 CFR 1.82(e-f) or 1.825(b) or 1.825(d). It is noted that Applicant will provide a new Sequence Listing and disc in a subsequent amendment.

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

11. The listing of references in the specification, such as the ones at pages 29-30, is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

12. The information disclosure statement filed May 2, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

13. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claims 1-2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, a product of nature. Amending the claims 1-2 to encompass an isolated peptide that does not occur in nature would obviate this rejection.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-3, 8-10, 15-16 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated peptide consisting of the amino acid sequence selected from the group of SEQ ID NO: 2, and SEQ ID NO: 3, a composition

comprising the isolated peptide consisting of the amino acid sequence of SEQ ID NO: 2, and SEQ ID NO: 3, or SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 and a pharmaceutical acceptable carrier for inhibiting HARP induced angiogenesis, **does not** reasonably provide enablement for (1) any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, or the sequence of 65-97 of any HARP factor; (2) any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 2, or SEQ ID NO: 3, and exhibiting any angiogenesis inhibiting activities and a capacity for binding to glycoaminoglycans (GAG); (3) any peptide in which the sequence differs from the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 by any conservative substitution of at least one amino acid; (4) any pharmaceutical composition comprising any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, the sequence of 65-97 of any HARP factor; (5) any pharmaceutical composition comprising any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, the sequence of 65-97 of any HARP factor further comprising any peptide having the sequence of amino acids 111-136 of any HARP factor or any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4; (6) any composition comprising the "peptide 13-39 of sequence SEQ ID NO: 2"; the "peptide 65-97 of sequence of SEQ ID NO: 3" and the "peptide 111-136 of sequence SEQ ID NO: 4" and (7) a method for the preparation of any medicament comprising adding any peptide mentioned above to a pharmaceutically acceptable vehicle as set forth in claims 1-3, 8-10, 15-16 and 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 1 and 8 encompass any peptide consisting of the amino acid sequence of amino acids selected from the sequence 13-39 of any HARP factor or the sequence 65-97 of any HARP factor or any pharmaceutical composition comprising such peptide.

Claims 2-3 encompass any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 or any sequence differs from the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 by having any conservative substitution.

Claims 9 and 16 encompass any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, the sequence of 65-97 of any HARP factor and further comprising any second peptide having the sequence of amino acids 111-136 of any HARP factor or any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4.

Claim 10 encompasses a composition comprising the "peptide 13-39 of sequence SEQ ID NO: 2"; the "peptide 65-97 of sequence of SEQ ID NO: 3" and the "peptide 111-136 of sequence SEQ ID NO: 4" and one or more pharmaceutical acceptable excipients.

Enablement is not commensurate in scope with any peptide and pharmaceutical composition comprising any peptides mentioned above.

The specification discloses only human HARP polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The specification discloses three human HARP peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 that correspond to amino acid residues 13-39, 65-97, and 111-136 of SEQ ID NO: 1, respectively. The specification discloses SEQ ID NO: 2 and SEQ ID NO: 4, which correspond to amino acid residues 13-39 and 65-97 of SEQ ID NO: 1, that bind to glycoaminoglycans (GAG) and inhibit HARP mediated angiogenesis, see page 28. The specification discloses peptide of SEQ ID NO: 4 binds to the anaplastic lymphoma kinase "ALK" receptor and inhibits angiogenesis. The specification defines the term "similar" to encompass any sequences which are perfect resemblance or identity between the amino acids compared but also to the imperfect resemblance which is defined as similarity. This search for similarities in a polypeptide sequence takes into account the conservative substitutions which are substitutions of amino acids of the same class, but also include "variant, homologue or derivative amino acid sequence" which differ from the reference sequence by substitution, deletion and/or insertion of an amino acid or a plurality of amino acids, preferably a reduced number of amino acids, particularly by substitution of natural amino acids by non-natural amino acids or pseudo-amino acids at positions such that

these modifications do not significantly undermine the biological activity of the peptides, see pages 7-8 of the specification. The intended use of the peptide is for treatment or prevention of any angiogenesis associated pathology such as benign or malignant tumor including melanomas, carcinomas, sarcomas, rhabdomyosarcoma, retinoblastoma, neuroblastoma, osteosarcoma. Amongst the solid tumours mention may be made in particular of tumours (primitive or not) of the breast, the ovary, the lung, the cervix, the digestive tract, in particular the colon, the urologic system, the liver, the pancreas, the bones. Non-solid tumours are equally covered, namely in particular leukaemias or lymphomas. The proliferative disorders can be treated at any stage in the proliferation. The peptides or the nucleic acids according to the invention are in particular useful for combating the development of tumoral metastases. Amongst the benign tumours mention may finally be made in particular of haemangiomas and hepatocellular adenomas, see page 15-16 of the specification.

However, the specification does not teach the sequence of amino acids 13-39 or 65-97 or 111-136 from any HARP factor other than human HARP comprising SEQ ID NO: 1 and whether such peptide inhibits angiogenesis. There is no guidance whether all the sequences of amino acids 13-39 or 65-97 and/or 111-136 from other HARP factor are identical to amino acids 13-39 or 65-97 or 111-136 of human HARP factor, let alone having the same function as human HARP factor. Further, there is insufficient guidance as to which position within the sequence of amino acids of SEQ ID NO: 2 or SEQ ID NO: 3 to be substitute, deleted, added or combination thereof such that the resulting peptide merely has "80% similar" to SEQ ID NO: 2 or SEQ ID NO: 3, respectively, still binds to glycoaminoglycans, let alone such peptide inhibits angiogenesis. Likewise, there is insufficient guidance as to the position within the sequence of amino acids of SEQ ID NO: 4 to be substitute, deleted, added or combination thereof such that the resulting peptide has at least "80% similar" to SEQ ID NO: 4 still binds to ALK receptor, much less such peptide inhibits angiogenesis. The term "comprising" or "having" is open-ended. It expands the undisclosed peptide having at least "80% similar" to SEQ ID NO: 2 or SEQ ID NO: 3 or SEQ ID NO: 4 to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added.

The state of the art as evidenced by the teachings of the US Pat NO 6,103,880 are such that biologically active peptides having such an N-terminal sequence are all the more unexpected since it would be difficult for a person skilled in the art to predict that an addition of amino acids to the N-terminal sequence of the known peptide such as HARP family growth factor would

improve its biological activity. The '880 patent teaches "in fact, predictions as to the effect of the addition, elimination or modification of amino acid in a given structure are impossible in the current state of knowledge of protein structures, even with the aid of the most advanced modeling technique" (see col. 3, lines 55-65, in particular).

Zhang et al (J Biol Chem 274(9): 12959-12962, 1999; PTO 892) teach various human pleiotrophin (also known as PTN or HARP) peptides and peptide-containing residues 41-64 of PTN induces tumor transformation (see entire document, Discussion, in particular). Zhang et al teach NIH 3T3 cells expressing PTN 1-40 which contains the claimed peptide comprising the amino acid residues 13-39 of HARP grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Likewise, NIT 3T3 cells expressing PTN 101-136 which contains the claimed peptide comprising residues 111-136 also grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Zhang et al teach it is unexpectedly that larger tumors were found at the sites of injection of NIH 3T3 cells expressing PTN peptide having deletion of the two internal repeats (residues 41-45 and 65-68), see page 12961, col. 1, in particular).

Further, given the numerous undisclosed peptides having no resemblance to SEQ ID NO: 2, SEQ ID NO: 3 and/or SEQ ID NO: 4 for the claimed pharmaceutical composition, there are insufficient *in vivo* working examples showing the claimed pharmaceutical composition comprising such peptides is efficacious for treating any and all tumor mentioned above, let alone for prevention of any and all tumor.

Pharmaceutical composition in the absence of *in vivo* data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With respect to claim 10, the sequences of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 are only 28, 33 and 26 amino acids in lengths, respectively. The recitation of the peptide 13-39 of sequence of SEQ ID NO: 2, the peptide 65-97 of SEQ ID NO: 3 and the peptide 111-136

of sequence SEQ ID NO: 4 is inappropriate because the amino acid residues 29-39, 65-97 and 111-136 are not found in SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, respectively. Because the peptides mentioned above are not enabled, it follows that the method of preparing a medicament using any such peptide is not enabled.

Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

17. Claims 1-3, 8-10, 15-16 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, or the sequence of 65-97 of any HARP factor; (2) any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 2, or SEQ ID NO: 3; (3) any peptide in which the sequence differs from the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 by any conservative substitution of at least one amino acid; (4) any pharmaceutical composition comprising any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, the sequence of 65-97 of any HARP factor; (5) any pharmaceutical composition comprising any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, the sequence of 65-97 of any HARP factor further comprising any peptide having the sequence of amino acids 111-136 of any HARP factor or any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4; (6) any composition comprising the "peptide 13-39 of sequence SEQ ID NO: 2"; the "peptide 65-97 of sequence of SEQ ID NO: 3" and the "peptide 111-136 of sequence SEQ ID

NO: 4" and (7) a method for the preparation of any medicament comprising adding any peptide mentioned above to a pharmaceutically acceptable vehicle as set forth in claims 1-3, 8-10, 15-16 and 19.

Claims 1 and 8 encompass any peptide consisting of the amino acid sequence of amino acids selected from the sequence 13-39 of any HARP factor or the sequence 65-97 of any HARP factor or any pharmaceutical composition comprising such peptide.

Claims 2-3 encompass any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 or any sequence differs from the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 by having any conservative substitution.

Claims 9 and 16 encompass any peptide consisting of the sequence of amino acids such as the sequence 13-39 of any HARP factor, the sequence of 65-97 of any HARP factor and further comprising any second peptide having the sequence of amino acids 111-136 of any HARP factor or any peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4.

Claim 10 encompasses a composition comprising the "peptide 13-39 of sequence SEQ ID NO: 2"; the "peptide 65-97 of sequence of SEQ ID NO: 3" and the "peptide 111-136 of sequence SEQ ID NO: 4" and one or more pharmaceutical acceptable excipients.

The specification discloses only human HARP polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The specification discloses three HARP peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 that correspond to amino acid residues 13-39, 65-97, and 111-136 of SEQ ID NO: 1, respectively. The specification discloses SEQ ID NO: 2 and SEQ ID NO: 4, which correspond to amino acid residues 13-39 and 65-97 of SEQ ID NO: 1, bind to glycoaminoglycans (GAG) and inhibit HARP mediated angiogenesis, see page 28. The specification discloses peptide of SEQ ID NO: 4 binds to the anaplastic lymphoma kinase "ALK" receptor and inhibits angiogenesis. The specification defines the term "similar" to encompass any sequences which are perfect resemblance or identity between the amino acids compared but also to the imperfect resemblance which is defined as similarity. This search for similarities in a polypeptide sequence takes into account the conservative substitutions which are substitutions of amino acids of the same class, but also include "variant, homologue or derivative amino acid sequence" which differ from the reference sequence by substitution, deletion and/or insertion of an amino acid or a plurality of amino acids, preferably a reduced number of amino acids, particularly by substitution of natural

amino acids by non-natural amino acids or pseudo-amino acids at positions such that these modifications do not significantly undermine the biological activity of the peptides, see pages 7-8 of the specification. The intended use of the peptide is for treatment or prevention of any angiogenesis associated pathology such as benign or malignant tumor including melanomas, carcinomas, sarcomas, rhabdomyosarcoma, retinoblastoma, neuroblastoma, osteosarcoma. Amongst the solid tumours mention may be made in particular of tumours (primitive or not) of the breast, the ovary, the lung, the cervix, the digestive tract, in particular the colon, the urologic system, the liver, the pancreas, the bones. Non-solid tumours are equally covered, namely in particular leukaemias or lymphomas. The proliferative disorders can be treated at any stage in the proliferation. The peptides or the nucleic acids according to the invention are in particular useful for combating the development of tumoral metastases. Amongst the benign tumours mention may finally be made in particular of haemangiomas and hepatocellular adenomas, see page 15-16 of the specification.

With the exception of the specific peptides consisting of SEQ ID NO: 2, 3 and 4, there is insufficient written description about the structure associated with function of any and all peptides as set forth in claims 1-3, 8-10, 15-16 and 19.

The specification discloses only one human HARP factor comprising SEQ ID NO: 1 and three peptides consisting of the amino acids residues 13-39 of SEQ ID NO: 1, residues 65-97 of SEQ ID NO: 1 and residues 111-136 of SEQ ID NO: 1. The specification does not adequately describe the residues 13-39, 65-97 and 111-136 of any other HARP factor, much less whether such peptide has the same function as the peptide consisting of the amino acids residues 13-39 of SEQ ID NO: 1, residues 65-97 of SEQ ID NO: 1 and residues 111-136 of SEQ ID NO: 1.

Further, there is inadequate written description about the position within the sequence of amino acids of SEQ ID NO: 2 or SEQ ID NO: 3 to be substitute, deleted, added or combination thereof such that the resulting peptide has at least "80% similar" to SEQ ID NO: 2 or SEQ ID NO: 3, respectively, still binds to glycoaminoglycans, let alone such peptide inhibits angiogenesis. Likewise, there is insufficient disclosure about the position within the sequence of amino acids of SEQ ID NO: 4 to be substitute, deleted, added or combination thereof such that the resulting peptide has at least 20% difference to SEQ ID NO: 4 still binds to ALK receptor, let alone such peptide still inhibits angiogenesis. The term "comprising" or "having" is open-ended. It expands the undisclosed peptide having at least "80% similar" to SEQ ID NO: 2 or SEQ ID

NO: 3 or SEQ ID NO: 4 to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added.

The state of the art as evidenced by the teachings of the US Pat NO 6,103,880 are such that biologically active peptides having such an N-terminal sequence are all the more unexpected since it would be difficult for a person skilled in the art to predict that an addition of amino acids to the N-terminal sequence of the known peptide such as HARP family growth factor would improve its biological activity. The '880 patent teaches "in fact, predictions as to the effect of the addition, elimination or modification of amino acid in a given structure are impossible in the current state of knowledge of protein structures, even with the aid of the most advanced modeling technique" (see col. 3, lines 55-65, in particular).

Zhang et al (J Biol Chem 274(9): 12959-12962, 1999; PTO 892) teach various human pleiotrophin (also known as PTN or HARP) peptides and peptide-containing residues 41-64 of PTN induces tumor transformation (see entire document, Discussion, in particular). Zhang et al teach NIT 3T3 cells expressing PTN 1-40, which contains the claimed peptide comprising the amino acid residues 13-39 of HARP, grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Likewise, NIH 3T3 cells expressing PTN 101-136, which contains the claimed peptide comprising residues 111-136, also grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Zhang et al teach it is unexpectedly that larger tumors were found at the sites of injection of NIH 3T3 cells expressing PTN peptide having deletion of the two internal repeats (residues 41-45 and 65-68), see page 12961, col. 1, in particular).

Further, given the numerous undisclosed peptides having no resemblance to SEQ ID NO: 2, SEQ ID NO: 3 and/or SEQ ID NO: 4 for the claimed pharmaceutical composition, there is no disclosure as to whether such peptides is efficacious for treating any and all tumor mentioned above, let alone for prevention of any and all tumor.

With respect to claim 10, the sequences of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 are only 28, 33 and 26 amino acids in lengths, respectively. The recitation of the peptide 13-39 of sequence of SEQ ID NO: 2, the peptide 65-97 of SEQ ID NO: 3 and the peptide 111-136 of sequence SEQ ID NO: 4 is inappropriate because the amino acid residues 29-39, 65-97 and 111-136 are not found in SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, respectively.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

As discussed above, the skill artisan cannot envision the detailed chemical structure of the encompassed genus of peptide of HARP factor for the claimed pharmaceutical composition, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The antagonist itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

Since the specification discloses only three peptides from only human HARP factor as set forth in SEQ ID NO: 2, 3 and 4, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of the sequence 13-39 or 65-97 or 111-136 of any HARP factor, peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 2, or SEQ ID NO: 3, peptide in which the sequence differs from the sequence of SEQ ID NO: 2 or SEQ ID NO: 3 by any conservative substitution of at least one amino acid, peptide comprising any sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4 and the "peptide 13-39 of sequence SEQ ID NO: 2"; the "peptide 65-97 of sequence of SEQ ID NO: 3" and the "peptide 111-136 of sequence SEQ ID NO: 4" for the claimed pharmaceutical composition. Applicant was not in possession of the claimed genus. Since the peptides mentioned above are not adequately described, it follows that the method of preparing a medicament using any such peptide is not adequately described.

Accordingly, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of compound to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Applicant is reminded that Vas-Cath makes clear that the

written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

19. Claims 10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of the peptide 13-39 of sequence of SEQ ID NO: 2, the peptide 65-97 of SEQ ID NO: 3 and the peptide 111-136 of sequence SEQ ID NO: 4 is indefinite and ambiguous because the sequences of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 are only 28, 33 and 26 amino acids in lengths, respectively. The amino acid residues 29-39, 65-97 and 111-136 are not found in SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, respectively. As such, the metes and bounds of such peptides cannot be determined. It is suggested that claim 10 be amended to recite the composition comprising the peptide consisting of the amino acid sequence of SEQ ID NO: 2, the peptide consisting of the amino acid sequence of SEQ ID NO: 3 and the peptide consisting of the amino acid sequence of SEQ ID NO: 4. Alternatively, the composition comprising the peptide consisting of amino acid residues 13-39 of SEQ ID NO: 1, the peptide consisting of amino acid residues 65-97 of SEQ ID NO: 1 and the peptide consisting of the amino acid residues 111-136 of SEQ ID NO: 1.

The term "associated with" in claim 16 is indefinite and ambiguous because the metes and bounds of what is meant by "associated with" cannot be determined. It is unclear whether the peptide of claim 15 is physically associated with (covalently linked to) a second peptide or noncovalently associated with such as peptides in a composition.

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Hampton et al (Molecular Biology of the Cell 3: 85-93, 1992; PTO 892).

Hampton et al teach a peptide such as heparin-binding growth-associated molecule (HB-BAM) comprising the amino acid sequence SDCGEWQWSVCVPTSGDCGLGTREGTR, which is 100% identical to amino acid residues 13-39 of the HARP factor or claimed SEQ ID NO: 2 (see page 89, sequence in Figure 2, residues 13-39 of the reference sequence, in particular). The reference HB-BAM also comprises the amino acid sequence AECKYQFQAWGECDLNTALKTRTGSLKRALHNA, which is 100% identical to the claimed SEQ ID NO: 3 (see page 89, sequence in Figure 2, residues 65 to 97, in particular). The term "comprising" is open-ended. It expands the claimed peptide to read on the reference peptide. Products of identical chemical composition cannot have mutually exclusive properties. The reference peptide inherently has the same activity such as exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG). A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, i.e., same amino acid sequence, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fec. Cir. 1990). See MPEP 2112.01. Thus, the reference teachings anticipate the claimed invention.

22. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,461,029 (issued Oct 1995; PTO 892).

The '029 patent teaches a peptide such as heparin-binding protein comprising the amino acid sequence SDCGEWQWSVCVPTSGDCGLGTREGTR, which is 100% identical to amino acid residues 13-39 of the HARP factor or claimed SEQ ID NO: 2 (see reference SEQ ID NO: 5, residues 13-40, in particular). The reference heparin-binding protein also comprises the amino acid sequence AECKYQFQAWGECDLNTALKTRTGSLKRALHNA, which is 100% identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, residues 65-97, in particular). The term "comprising" is open-ended. It expands the claimed peptide to read on the reference peptide. The reference further teaches pharmaceutical composition comprising the reference heparin-binding protein and a pharmaceutically acceptable carrier such as phosphate buffered

saline water, methyl cellulose (see col. 3, lines 17-21, in particular). Thus, the reference teachings anticipate the claimed invention.

23. Claims 1-3, 15-16 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/083851 publication (published Oct 24, 2002; PTO 892).

The WO 02/083851 publication teaches a peptide such as AAE32362 consisting of the amino acid sequence of amino acids AECKYQFQAWGECDLNTALKTRTGSLKRALHNA, which is 100% identical to the claimed sequence of 65-97 of the HARP factor (see sequence alignment below, page 28, paragraphs 67-38, reference SEQ ID NO: 36 in particular). The term "comprising" is open-ended. It expands the claimed SEQ ID NO: 3 to include additional amino acids at either or both ends. The publication further teaches fusion protein comprising the reference heparin-binding peptide fused to angiogenic factor such as VEGF or anti-angiogenic factor such as angiogensin, see page 76, paragraphs 183-185, in particular).

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PN   WO200283851-A2.
XX
PD   24-OCT-2002.

SQ   Sequence 54 AA;

  Query Match             100.0%;  Score 180;  DB 6;  Length 54;
  Best Local Similarity   100.0%;  Pred. No. 1e-18;
  Matches   33;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 AECKYQFQAWGECDLNTALKTRTGSLKRALHNA 33
              |||||||||||||||||||||||||||||||||
Db          1 AECKYQFQAWGECDLNTALKTRTGSLKRALHNA 33
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The publication teaches conservative substitutions to the reference HBNF, see pages 8-9, pages 28-30, in particular). The publication further teaches a method of preparing a pharmaceutical composition by putting the reference peptide and a pharmaceutical acceptable carrier together (see page 64, paragraphs 152-153, page 77, paragraph 189-185, in particular). The WO 200283851 publication teaches the reference composition is useful for treating various diseases such as anti-inflammation, rheumatoid arthritis, osteoarthritis, to improve poor bone healing, to promote implant integration and function of artificial joints and to facilitate bone reconstruction (see 77, paragraph 183, paragraph 185, in particular). Claim 16 is included in this rejection because the reference also teaches the reference fusion protein further comprises a full-length peptide having 100% sequence identity to the claimed peptide having the sequence of

amino acids 111-136 of the human HARP factor (see reference SEQ ID NO: 33, page 30, paragraph 72, in particular). Again, the term "having" is open-ended. It expands the claimed peptide of SEQ ID NO: 4 to include additional amino acids at either or both ends. Thus, the reference teachings anticipate the claimed invention.

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. Claims 1, and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 200283851 publication (published Oct 24, 2002; PTO 1449) in view of US Pat No 6,103,880 (issued August 15, 2000; PTO 892) and/or Bernard-Pierrot et al (J Biol Chem 277 (35): 32071-32077; August 30, 2002; PTO 892).

The teachings of the WO 200283851 publication have been discussed supra.

The invention in claim 9 differs from the teachings of the reference only in that the composition further comprising a peptide having the amino acids 111-136 of the HARP factor or a peptide comprising a sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4.

The invention in claim 16 differs from the teachings of the reference only in that the method for the preparation of a medicament further comprising a second peptide having the amino acids 111-136 of the HARP factor or a peptide comprising a sequence of amino acids at least 80% similar to the sequence of SEQ ID NO: 4.

The '880 patent teaches a heparin-binding growth-associated molecule (HB-BAM) of SEQ ID NO: 2 comprising the amino acid sequence KPKPQAESKKKKKEGKKQEK, which is 100% identical to the claimed SEQ ID NO: 4 (see reference SEQ ID NO: 2, residues 114-139, in particular). The term "having" is open-ended. It expands the claimed SEQ ID NO: 4 to include additional amino acids at either or both ends. Given the reference peptide having the same structure as the claimed peptide, the recited activity is an inherently property of the reference peptide such as exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG). A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, i.e., same amino acid sequence, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fec. Cir. 1990). See MPEP 2112.01.

Bernard-Pierrot et al teach a truncated heparin affin regulatory peptide corresponding to 111-136 of HARP, which consisting of the amino acid sequence of KPKPQAESKKKKKEGKKQEK, and is 100% identical to the claimed SEQ ID NO: 4 (see page 32072, col. 1, Experimental Procedures, in particular). The reference peptide inhibits angiogenic activity induced by HARP (see page 32072, col. 2, Figure 2E, in particular). Bernard-Pierrot et al teach HARP is expressed in many human tumors such as neuroblastoma, melanoma, pancreatic and breast cancer and this molecule is now considering an interesting target in cancer therapy (see page 32076, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine HARP family of growth factors as taught by the WO 200283851 publication with the heparin-binding growth-associated molecule as taught by the '880 patent or the heparin affin regulatory peptide as taught by Bernard-Pierrot et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine these HARP peptide for the preparation of a medicament because Bernard-Pierrot et al teach HARP is expressed in many human tumors such as neuroblastoma, melanoma, pancreatic and breast cancer and this molecule is now considering an interesting target in cancer therapy (see page 32076, col. 1, in particular). The WO 200283851 publication teaches the composition comprising the reference HARP peptide is useful for treating various diseases such as rheumatoid that involved angiogenesis (see abstract, in particular).

27. Claim 10 appears to be free of prior art.

28. No claim is allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

30. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
November 9, 2007

Notice to Comply	Application No. 10/533,443	Applicant(s) County et al
	Examiner Phuong N. Huynh	Art Unit 1644

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See item 9 of Office Action.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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